

# Interactions of Ku70/80 with double-strand DNA: energetic, dynamics, and functional implications

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Space radiation is a proficient inducer of DNA damage leading to mutation, aberrant cell signaling, and cancer formation. Ku is among the first responding proteins in nucleus to recognize and bind the DNA double strand breaks (DSBs) whenever they are introduced. Once loaded Ku works as a scaffold to recruit other repair factors of non-homologous end joining and facilitates the following repair processes. The crystallographic study of the Ku70/80 heterodimer indicate the core structure of this protein shows virtually no conformational change after binding with DNA. To investigate the dynamical features as well as the energetic characteristics of Ku-DNA binding, we conduct multi-nanosecond molecular dynamics simulations of a modeled Ku70/80 structure and several complexes with two 24-bp DNA duplexes. Free energy calculations show significant energy differences between the complexes with Ku bound at DSBs and those with Ku associated at an internal site of a chromosome. The results also reveal detailed interactions between different nucleotides and the amino acids along the DNA-binding cradle of Ku, indicating subtle binding preference of Ku at specific DNA sequences. The covariance matrix analyses along the trajectories demonstrate the protein is stimulated to undergo correlated motions of different domains once bound to DNA ends. Additionally, principle component analyses identify these low frequency collective motions suitable for binding with and translocation along duplex DNA. It is proposed that the modification of dynamical properties of Ku upon binding with DSBs may provide a signal for the further recruitment of other repair factors such as DNA-PKcs, XLF, and XRCC4.